COMPOSITIONS AND METHODS FOR REDUCING TACTILE DYSFUNCTION, ANXIETY, AND SOCIAL IMPAIRMENT

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application, U.S. Ser. No. 62/674,770, filed on May 22, 2018, and to U.S. Provisional Application, U.S. Ser. No. 62/823,360, filed on Mar. 25, 2019, each of which is incorporated herein by reference in their entirety.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

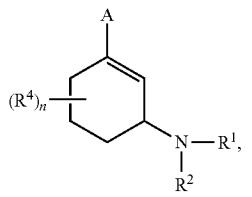
[0002] This invention was made with government support under Grant Nos. NS101057 and NS97344 from the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Autism spectrum disorder (ASD) is a highly prevalent class of neurodevelopmental disorders characterized by impairments in social communication and interactions, as well as restricted and repetitive behaviors. Rates of ASD diagnoses are increasing, and the CDC identifies one in every 59 children in the United States as having ASD. In the United States alone, it is estimated that the ASD-related healthcare costs exceed 230 billion dollars per year, or 1.4 million per individual with ASD over their lifetime. A majority of ASD patients (60.9%) report altered tactile sensitivity in both glabrous (smooth) and hairy skin, and altered sensitivity to vibration and thermal pain. As with idiopathic or non-syndromic ASD, pervasive developmental disorders that cause syndromic forms of ASD are also associated with disrupted somatosensation. For example, abnormalities in tactile perception are observed in patients with Phelan McDermid Syndrome (PMS) and Fragile X syndrome, which are both highly associated with ASD and are caused by mutations in Shank3 and Fmr1, respectively Similarly, tactile hypersensitivity is common in patients with Rett syndrome (RTT), which is caused by mutations in the X-linked methyl-CpG-binding protein 2 (Mecp2) gene. There is an inverse correlation between the presence of ASD traits in human subjects and their neural responses to C-low-threshold mechanoreceptor (LTMR)-targeted affective touch. Currently, there are no FDA-approved treatments for ASD. Thus, a critical need exists for novel therapeutic approaches to treat ASD and related disorders such as Rett syndrome, Phelan McDermid Syndrome, and Fragile X syndrome.

SUMMARY OF THE INVENTION

[0004] In one aspect, the invention features a compound having the structure of Formula (I):



(I)

wherein

[0005] n=1, 2, 3, 4, 5, 6, 7, or 8;

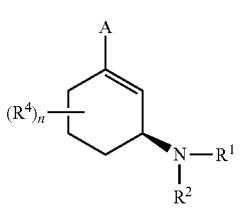
[0006] each of R^1 and R^2 is, independently, hydrogen, deuterium, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} cycloalkyl, wherein R^1 and R^2 are covalently linked;

[0007] each R^4 is, independently, hydrogen, deuterium, halogen, C_{1-4} alkoxy, C_{1-6} alkyl, CF_3, CH_3S, CH_3SO_2, or NO_2; and

[0008] A is a carboxylic acid, a carboxylic acid biomimetic, or optionally substituted C_{1-6} carboxylic acid alkyl ester;

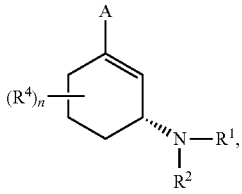
or a pharmaceutically acceptable salt thereof.

[0009] In some embodiments, the compound has the structure of Formula (Ia) or (Ib):



(Ia)

or



(Ib)

or a pharmaceutically acceptable salt thereof.

[0010] In some embodiments, A is a carboxylic acid, optionally substituted C_{1-6} carboxylic acid alkyl ester, or has the structure of: